POSTER: CLINICAL TRACK: CNS AND HAEMATOLOGY

PO-0655

Stereotactic RT of recurrent high-grade glioma based on FET-PET and MRI: Initial results of a dose escalation trial

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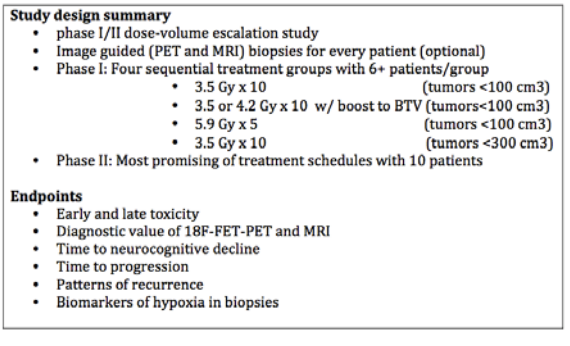
Purpose/Objective: Re-irradiation of high-grade glioma (HGG) using modern delivery techniques and advanced imaging 18F-flouroethyl-tyrosine (FET)-PET and MRI have not been systematically evaluated. The initial results of a prospective, FET-PET and MRI-guided, dose-escalation study of previously irradiated HGG are presented.

Materials and Methods: Patients with performance status 0-2 with localized disease progression despite standard therapy were eligible to be included. The target was defined using MRI (Siemens 1.5 T scanner, T1 w/Gd contrast) and FET-PET (Siemens mCT brain scanner 20 min after injection of 200 MBq FET, threshold: 1.6 of SUV mean in background) and these volumes were fused. A 2 mm PTV (planning target volume) margin was added. Hypofractionated stereotactic radiotherapy (SRT) was planned in Eclipse dose planning system (Varian) and given as Volumetric Modulated Arc Therapy on a Novalis Tx accelerator (Varian/BrainLab). Total doses to organs at risk (brainstem, optic chiasm) were calculated using primary and current treatment plans.

Results: Fifteen patients were referred to treatment in dose level one (3.5 Gy x 10, 5 F/W) between December 1, 2011 and August 1, 2012. Twelve were eligible to be included. Histological diagnoses were glioblastoma multiforme (83%) and anaplastic astrocytoma WHO grade III. All patients had received prior focal radiotherapy (44 Gy-60 Gy) and the median interval since primary RT was 26.7 months (range: 14.3-67.7 months). In 11/12 cases increased FET uptake consistent with malignant disease was detected. The median GTV MR (defined by T1 MR with contrast) was 23.8 cm3 (range: 7.9-52.4 cm3). The combined GTV used for planning (based on MRI and PET) was larger than the GTV MR for 11 out of 12 patients by a median of 26% (range: 0-283%). The median PTV volume was 53.4 cm3 (range: 21.1-91.3 cm3). The median doses to chiasm and brainstem were 0.9 (range: 0.2-22.8 Gy) and 1.2 (range: 0.4-26.9 Gy) in 2-Gy equivalent fractions ($\alpha/\beta=3$), respectively. Doses to the chiasm and brainstem exceeded 15 Gy in 1 and 2 cases of temporal tumors, respectively. All patients completed treatment as planned. No serious (grade 2+ CTC) acute adverse events were observed during treatment or in the 4 following weeks. One patient experienced dizziness and unilateral motor dysfunction 4 weeks after treatment. Disease progression was suspected but the patient withdrew from the study. No serious late side effects have been observed. Minimum follow-up time for all (surviving) patients is currently 3 months.

Conclusions: Re-irradiation using 3.5 Gy x 10 to localized recurrences of HGG using MR and FET-PET for target delineation was feasible and well tolerated. Using FET-PET for target delineation increased the size of the GTV by a median of 26%. Only in case of temporal tumors did doses to organs at risk pose a planning challenge. The study is ongoing and has now progressed to the next escalated dose-level.



PO-0656

Dose intensified irradiation to brain metastases or resection cavity and low dose prophylactic cranial irradiation

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Purpose/Objective: Standard therapy for patients with brain metastases was WBRT with 30Gy/10fx in our institution. We report about our newly developed radiotherapy procedure with hypofractionated dose intensification to metastases with or without simultaneously applied low dose prophylactic cranial irradiation (PCI) to the remaining brain.

Materials and Methods: From 6/2010 until 5/2012 61 patients with 1-4 brain metastases and Karnofsky performance score > 50 were treated with our new therapy concept. 21 Patients received local treatment only whereas 40 patients assumed to have a higher risk for new distant brain metastases were treated with simultaneous low dose PCI. 20 patients were irradiated after gross tumour resection. Macroscopic metastases were treated to 60Gy/15fx (BED10 84Gy, BED3 140Gy) and PCI was applied with 27Gy/15fx (BED10 32Gy, BED3 43Gy) using RapidArc technique with simultaneous integrated boost (SIB). Following resection of the metastasis the resection cavity was irradiated to 48Gy/15fx (BED10 63Gy), residual/unresected macroscopic tumour to 60Gy/15fx and the remaining brain if indicated to 27Gy/15fx (PCI). CTV was equal to GTV and a 3-5 mm margin was used for the PTV PTV. The minimum dose for the metastases was 95% of the prescribed dose, whereas the median dose for the whole brain was 27 Gy. All patients were followed prospectively with CT or MRI scan every 2-4 months until deterioration. Toxicity was assessed by the treating physician using CTCAE 4.0. Statistical analysis was performed with Kaplan Meier and Logrank test. Multivariate analysis was performed using Cox-regression.

Results: The median follow-up was 10.7 months (range 4.1-26.1 months). The treatment was well tolerated and no grade 3 or higher acute toxicity was observed. One patient with 4 small metastases who was treated with 60Gy/15fx and PCI died possibly due to progressive radionecrosis 15 months after treatment. Local recurrence-free survival after treatment with 60Gy/15fx has been 100%, whereas one metastasis relapsed after resection and postoperative RT (48Gy/15fx). Regional recurrence-free survival within 9 months was 68% with PCI and 59% without PCI, respectively (p=0.23). 39 patients died during follow-up and the overall survival at 12 months was 44%. Median survival time in univariate analysis was significantly better for patients younger than 60 years (13.0 vs. 7.5 months, p=0.03), patients with RPA I (18 vs. 7.6 months, p=0.005), patients with controlled extracranial disease (15 vs. 7 months, p=0.005) and patients who received PCI (11.5 vs. 6.3 months, p=0.02). Gross tumour resection and solitary metastasis did not result in significantly better survival. In multivariate Cox regression analysis RPA I class and PCI remained statistically significant predictors for improved survival.

Conclusions: Dose intensified irradiation to macroscopic brain metastases or resection cavities can be combined with a well tolerated prophylactic cranial irradiation using SIB. Local tumour control appears to be excellent, distant brain failure was moderate and overall survival was promising.

PO-0657

Radiotherapy plus dose escalation temozolomide in primary central nervous system lymphoma: final report

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Purpose/Objective: To define the maximum tolerable dose (MTD) of temozolomide concomitant to radiotherapy in patients with Primary Central Nervous System Lymphoma (PCNLSL), previously treated with high dose Methotrexate (HD-MTX).

Materials and Methods: Patients (≥18 yrs) with histologically proven diagnosis of PCNSL, treated with two cycles of HD-MTX, were enrolled. For radiation treatment, Clinical Target Volumes (CTVs) were: whole brain plus leptomeninges until C2 (CTV2) (30 Gy in 15 fractions), and initial site of disease plus residual mass if present (CTV1) (3600-4600 cGy depending on HD-MTX response). Dose escalation of concomitant Temozolomide (TMZ) until standard concomitant to radiotherapy dose advanced using a standard 3+3

design; 3 level dose were tested: 50-60-75 mg/mq/die for 5 days/week. Primary endpoint was to define the Maximum Tollerate Dose (MTD); acute toxicity (RTOG/EORTC) considered dose-limiting was: any grade ≥4 hematological toxicity or any grade 3 or 4 hepatic toxicity. Secondary endpoint were clinical outcomes in terms of radiation therapy response rate, disease free survival (DFS) and overall survival (OS).
Results: From April 2007 to June 2011, 9 patients were enrolled: 5 male and 4 female. Median age was 67 yrs (range 50-76). IELSG at diagnosis was 0 in 2 patients, 1 and 2 in three patients respectively, 4 in only one patients. Three of nine patients received only one cycle of HD-MTX because of hepatic, renal and haematological toxicity respectively. Seven patients had single lesion while 2 patients had multiple lesions; total lesions were 12. After HD-MTX 4/12 lesions had unconfirmed complete response (CRu), 5/12 had partial response (PR) and 3 showed progressive disease (PD). None dose-limiting toxicities was recorded. Acute toxicity was very low: one patients developed grade 2 white blood cells toxicity, and two patients developed grade 1 hepatic toxicity. At a median follow up of 43 months, (range 18-69) 6/9 patients (66.6%) are alive without disease, two older patients died because of disease and one patients died because of other causes. Median OS is 50 months with at 3 yrs OS of 78%. Median DFS has not yet reached, while at 3-yrs DFS is 74%.
Conclusions: The MTDs for the combination of RT and Temozolomide after HD-MTX was not reached; standard dose of Temozolomide (75 mg/mq/die) can be safely used associated to radiotherapy. Further studies are warranted to define clinical outcomes.

PO-0658
Adaptive hybrid surgery: feasibility study of computer-assisted multi-modality approach to skull base tumors
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Purpose/Objective: Complex skull base tumors, such as large meningiomas and schwannomas, pose unique management challenges because of their irregular shapes, proximity and involvement of critical normal structures, and variable tumor volumes. Surgical decompression is often desired to relieve mass effect on brainstem and other critical structures, including cranial nerves, but gross total removal is often not possible without significant neurologic morbidity. We present preliminary outcomes of a feasibility study of planned subtotal resection with intelligent, computer-assisted, intra-operative guidance (*Adaptive Hybrid Surgery*) for management of these patients.
Materials and Methods: To date, five patients with complex skull base tumors (2 large vestibular schwannomas, and 3 petroclival meningiomas) underwent computer-assisted, planned subtotal resection (STR), three of which were staged resections, followed by adjuvant stereotactic radiotherapy (SRT) or radiosurgery (SRS). Pre-operative RT plans (designed to maximize tumor coverage) were uploaded into cranial navigation and stereotactic planning system. Resection approach and goals were planned pre-operatively, and extent of resection (EOR) was defined intraoperatively, iteratively, and in real-time by the operating neurosurgeon. Expected post-operative SRT or SRS toxicity was estimated in near real-time using a set of pre-defined parameters during surgery to inform and guide resection extent with the aim of sculpting the tumor to create an ideal radiosurgical target. When estimates of post-op RT toxicity met predefined criteria, resection was halted and patients went on to received post-operative RT (within 1 month of surgery).
Results: Pathologic review of surgical specimens was consistent with benign tumor histology in all five cases. Pre- and post-operative RT planning was performed successfully in all cases; without surgical resection, all 5 lesions would require conventionally-fractionated SRT in the adjuvant setting; however, 3 cases were eligible for (and successfully converted to) a 5-day SRS treatment following computer-guided tumor debulking and were treated in that manner. With median follow-up period of 20.0 months (range, 6-31 months), no tumor recurrences were observed and all patients experienced stable or improved neurologic function (one stable, 4 improved) compared to pre-operative baseline.
Conclusions: We have demonstrated the feasibility of adaptive, multi-modality management of complex skull base tumors with intra-operative software guidance. The approach of guided and selective 'tumor sculpting' in the setting of subtotal resection with planned adjuvant SRT is expected to result in tumor control rates that are in line with historical data, and has the potential to convert cases of adjuvant conventionally-fractionated SRT to SRS cases, thereby decreasing overall treatment time while minimizing both surgical and radiotherapy morbidity.

PO-0659
Concomitant maintenance TMZ and low dose radiation therapy after hypofractionation in naive unresectable GBM
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Purpose/Objective: To assess safety and efficacy of hypofractionated therapy followed by low dose radiation therapy (LDRT) combined with Temozolomide in adults with newly diagnosed Glioblastoma Multiforme (GBM).
Materials and Methods: Patients (KPS ≥ 70, age ≥18 years) who underwent to biopsy or who presented gross residual tumor after surgery were enrolled. Hypofractionated dose (30 Gy in ten fractions) combined with Temozolomide (75 mg/m^2 daily from start to end RT) was delivered before LDRT. Beginning with second adjuvant TMZ (200 mg/m^2 daily for 5 days every 28 days) patients received two daily doses of 0.40 Gy, at least 4 hours apart, for 5 days; 2-4 cycles were planned. Conformal irradiation included the tumor bulk with surgical cavity, plus a 30-mm margin. The primary endpoints as safety, toxicity and tolerability were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0. The secondary endpoints were the response, according to the RECIST Guidelines, the overall survival (OS) and the progression-free survival (PFS) calculated by the Kaplan-Mayer method.
Results: From June 2008 to January 2012, 20 patients (M/F: 1), with a median age was 64.5 years (range 43-75), were enrolled. All patients received the prescribed dose of 30 Gy. The median dose of LD-FRT was 12 Gy (range 3-24 Gy), equal to two cycles; 11/20 (55%) underwent to ≤2 cycles and 9/20 (45%) to > 2 cycles. All toxicities were reversible and only 5 patients (25%) presented hematologic toxicity, grade 1-2 of leukopenia and thrombocytopenia in 4/5 patients. Regarding the whole sample median OS and PFS from initial diagnosis were 18 and 11 months, respectively. According to the number of cycles, a median OS of 8 months and PFS of 5 months was observed in patients underwent to ≤2 cycles while a median OS of 27 months and PFS of 12 months when four cycles were administered.
Conclusions: Hypofractionated regimen followed by LDRT combined with TMZ is safe, well tolerated and may prolong the survival of patients with GBM. Further investigation is warranted; a new trial with different hypofractionated and LDRT dose is ongoing.

POSTER: CLINICAL TRACK: HEAD AND NECK

PO-0660
Cyberknife stereotactic body radiotherapy: a noval approach for the boost of oropharyngeal cancer
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Purpose/Objective: Prospective evaluation of outcomes, toxicity, and quality-of-life of patients with oropharyngeal cancer (OPC) treated by IMRT and stereotactic body radiotherapy boost.
Materials and Methods: Between 2004 and 2011, 132 consecutive patients with T1-4N0-3 OPC were treated with (chemo)radiotherapy with 46-Gy of IMRT to the primary tumor and the neck followed by a boost to the primary tumor by means of the Cyberknife (stereotactic body radiotherapy). Patients with node-positive disease received neck dissection 2-3 weeks after finishing radiotherapy. Endpoints were locoregional control (LRC), disease-free survival (DFS), and overall survival (OS), toxicity using Common Terminology Criteria for Adverse Events v3.0 (CTCAE) and QoL-assessment using the EORTC QLQ-C30 and QLQ-H&N35.
Results: After a median follow-up of 30 months, the 3-year actuarial incidence of LRC, DFS, and OS were 93, 85%, and 76%, respectively. Nine locoregional failures were reported. No single failure was observed in patients with T1 or T2 and in patients with HPV-related disease. At the end of treatment, 26% of patients had tube feeding. On the mutltivariate analysis tumor stage, chemotherapy and unilateral neck irradiation were significantly correlated with tube feeding. For the whole group, the overall incidence of grade ≥2 late toxicity was 23%. The incidence of grade ≥2 late dysphagia and